REMARKS

This paper is responsive to the Office Action dated December 15, 2004, which is the third action on the merits of the application. Claims 13-40 are pending in the application, and stand variously rejected. The rejection has been made final.

Amendments

Certain claims have now been amended as indicated above, but no claim has been cancelled or added. Reference to pPS derived cell populations comprising 40% hepatocyte lineage cells is supported in the specification as filed *inter alia* on page 18, line 39. The skilled reader will understand that the other 60% of the population is unspecified, and may or may not also have characteristics of hepatocyte lineage cells. Cell populations exemplified in the disclosure show as much as about 99% staining for hepatocyte markers (e.g., Table 13), and are covered by independent claims 13, 27, and 28 as amended, besides others.

Further consideration and allowance of the application is respectfully requested.

Interview

The undersigned is grateful to Examiner Thái-An N. Ton and Examiner Joseph Woitach for the courtesy of several interviews at the Patent Office on March 2, 2005, regarding this and other applications relating to human pluripotent stem cells.

The amendments and remarks presented here were discussed at the interview. The application is now believed to be in condition for allowance, which is respectfully requested.

Double Patenting

The pending claims stand provisionally rejected for obviousness-type double patenting over certain claims of copending application USSN 10/087,142.

A final Office Action has just been prepared for the 10/087,142 application. Accordingly, it is expected that the present application will issue as a U.S. Patent first, and no terminal disclaimer is required.

The pending claims also stand rejected for obviousness-type double patenting over claims 1-3 of U.S. Patent 6,458,589. The Office Action indicates that the claims in the present application are obvious because the cell populations of the '589 patent have the same characteristics as cells produced by the methods of the instant claims.

Applicant respectfully disagrees. In making this rejection, the Office has applied a two-way obviousness test. As explained in MPEP § 804 (II)(B)(1)(a), only a one-way test is permitted where the application being challenged was filed later than the issued patent. The only question is whether the claims of the present application are obvious with respect to the claims of the previously issued patent (without reference to what is disclosed in the specification).

The claims in the '589 patent cover a product: namely, a set of cell populations, one of which has certain characteristics of hepatocytes. The claims of the present application cover methods for making such cells *using a histone deacetylase inhibitor*. Nowhere in the claims of the '589 patent does it suggest that the hepatocyte lineage cells can be generated using a histone deacetylase inhibitor.

Thus, upon application of the one-way test, there is no obviousness type double patenting for the claims in the present application. Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112

Applicant acknowledges with gratitude that the previous enablement rejection for differentiation of the pPS cells before use of the histone deacetylase inhibitor, as an optional step, has been removed.

The pending claims now stand rejected under 35 USC § 112 ¶ 1 as not being enabled for making hepatocytes from pPS cells with histone deacetylase inhibitors other than 5 mM butyrate. The Office Action refers again to the article by Lee et al. (Genesis 38:32, 2004) as teaching that the effect of butyrate on embryonic stem cell differentiation is dose-dependent.

Applicant respectfully disagrees. It is unnecessary for the claims to indicate the concentration of butyrate needed to effect differentiation into hepatocyte lineage cells. The specification exemplifies butyrate concentrations that are effective. Should the reader decide to deviate from the exemplified concentration, this can be done without undue experimentation — the protocol is just repeated with the altered butyrate concentration, and the cell culture is monitored for the presence of hepatocyte lineage cells having the characteristics required by the claim. A working range of effective concentrations can easily be determined by titrating the concentration and monitoring the results in this fashion.

In the spirit of this explanation, the claims have been amended to indicate that the histone deacetylase inhibitor is present in *an effective concentration*.

By the same process, the skilled reader can determine without undue experimentation what other histone deacetylase inhibitors are also effective in making hepatocyte lineage cells from pPS cells. The working examples in the specification show that the process can also be done successfully using Trichlostatin A (claim 18 and claim 33), propionic acid, isovaleric acid, or isobutyric acid (claim 17). The evidence shows that histone deacetylase inhibitors *as a general class* can be used to make hepatocyte lineage cells according to the claimed method, *if titrated to an effective concentration.* The Office has offered no data that refutes this assertion.

Furthermore, as a principle of law, genus claims are allowed to read on inoperative species, providing the operative species can be identified without undue experimentation. In effect, the claim as amended covers only operative embodiments, since an agent that does not generate the hepatocyte lineage cells could not be used in an *effective concentration.*

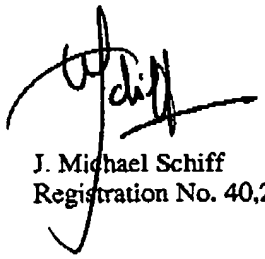
As suggested by the Examiners, the claims have also been amended so as to require the resulting cell population to comprise at least 40% hepatocyte lineage cells. By this criteria, the assay to determine the effectiveness of a histone deacetylase inhibitor for this purpose is even more simple to perform. Of course, the user may decide to select inhibitors, titrate concentrations, and adjust conditions to obtain populations that show much higher frequency of hepatocyte markers, as illustrated in the working examples, and still fall within the scope of the claimed invention.

Withdrawal of this rejection is respectfully requested.

Fees Due

No fee is believed due for entry or consideration of this Amendment. Nevertheless, should the Patent Office determine that an extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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